Answer 1:

Bibliographic Information

Aromatase inhibitory activity of newly developed hexamethylmelamine derivatives. Tanino, Hirokazu. Dep. Thorac. Cardiovasc. Surg., Wakayama Med. Coll., Wakayama, Japan. Wakayama Igaku (1996), 47(4), 427-432. Publisher: Wakayama Igakkai, CODEN: WKMIAO ISSN: 0043-0013. Journal written in Japanese. CAN 127:117154 AN 1997:396855 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Newly developed aromatase inhibitors (SAE 9, SEF 19 and SEF 32) were assessed by in vitro enzyme assay, in vivo uterine growth assay and the nude mouse-human breast carcinoma xenograft model and compared to aminoglutethimide (AMG). On the in vitro assay, the 50% inhibitory concn. (IC50) for aromatase of SAE 9, SEF 19, and SEF 32 were approx. 70, 7200, and 610 times higher than that of AMG, resp. The specificity to aromatase of the agent was assessed by the ratio of IC50 against aromatase to that against desmolase, which were 5.8 × 10-1 for AMG, <6.9 × 10-3 for SAE 9, <6.9 × 10-5 for SEF 19 and 6.5 × 10-3 for SEF 32. The androstenedione-stimulated rat uterine growth was suppressed by the same dose of SAE 9 and 1/100 dose of SEF 19 as AMG. Estrogen receptor pos. human breast carcinoma xenografts, T-61 were used for in vivo antitumor assay. The inhibition rates (%) of AMG, SAE 9, SEF 19, and SEF 32 were 54.0, 13.4, 71.2, and 54.1, resp. SEF 19 was specific and strong aromatase inhibitor according to the results of this screening test, and, this agent is thought to be promised aromatase inhibitor to treat the breast cancer patient clin.

Answer 2:

Bibliographic Information

Preclinical evaluation of aromatase inhibitors antitumor activity. Auvray P; Bichat F; Genne P Oncodesign Biotechnology, Parc technologique de la Toison-d'Or, 28, rue de Broglie, 21000 Dijon, France Bulletin du cancer (2000), 87 Spec No 7-22. Journal code: 0072416. ISSN:0007-4551. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE); General Review; (REVIEW) written in French. PubMed ID 11250604 AN 2001184265 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Aromatase is an enzymatic complex responsible for the conversion of androgens into estrogens; these hormones are important in development, reproduction, but also in the growth of estrogen-dependent cancer. This enzyme is present in 60-70% of the breast cancer. The aromatase inhibitors are important drugs in the breast cancer treatment of postmenopausal women. In order to study their in vivo activity, animal models have been developed, e.g. rat with tumour induced by 7,12-dimethylbenz[a]anthracene, PMSG-primed immature rat or athymic nude mice with aromatase transfected MCF-7 xenograft. In this review, we were interested in preclinical results obtained with both classes: steroidal and nonsteroidal inhibitors. The former group, as substrate analogs formestane or exemestane, are irreversible, selective and long-lasting inhibitors of aromatase. The nonsteroidal molecules, such as letrozole or anastrozole, are reversible inhibitors with high affinity. Finally, knowledge of the enzyme active site, with molecular modeling and site-directed mutagenesis, could be useful to develop new inhibitor families, more specific and potent in vivo.

Answer 3:

Bibliographic Information

The control and biological importance of intratumoural aromatase in breast cancer. Dowsett M; Lee K; Macaulay V M; Detre S; Rowlands M; Grimshaw R Royal Marsden Hospital, London, U.K The Journal of steroid biochemistry and molecular biology (1996), 56(1-6 Spec No), 145-50. Journal code: 9015483. ISSN:0960-0760.

Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T); General Review; (REVIEW) written in English. PubMed ID 8603035 AN 96184198 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The existence of aromatase activity in human breast carcinomas has been established for about 20 years but the clinical and biological importance of this remains unclear. A number of studies in clinical material suggest that aromatase activity may be a prerequisite of response to aromatase inhibitors and that aromatase activity may be enhanced in those tumours relapsing during treatment with one such inhibitor, aminoglutethimide. These results would carry more significance, however, if it was demonstrable that the growth of breast carcinomas is affected by the conversion of androgens to oestrogens by intratumoural aromatase. We have tried to address this by establishing model systems with aromatase-transfected MCF7 breast cancer cells. We have demonstrated that these cells can be stimulated mitogenically with androgen and that this proliferation is suppressible with aromatase inhibitors. Similarly the growth of aromatase transfected cells but not wild type cells as xenografts is supported by androstenedione and inhibitable by both the steroidal aromatase inhibitor, 4-hydroxyandrostenedione and non-steroidal inhibitor, CGS 20267. Work with the former of these, which is a suicide inhibitor allowed us to demonstrate that growth can proceed with aromatase activity approximating to the highest level seen in breast carcinomas indicating that at least at this extreme level the intratumoural conversion of androgens to oestrogens may indeed be able to support tumour growth. Further work with this mode system should allow us to define the minimal amount of intratumoural activity which can support tumour growth.

Answer 4:

Bibliographic Information

Experimental combined hormone therapy on human breast carcinomas serially transplanted into nude mice. Fukutomi T; Kubota T; Ikeda T; Isobe Y; Kikuyama S; Shimada A; Nakamura A; Nishiumi T; Enomoto K; Ishibiki K; + Japanese journal of cancer research : Gann (1986), 77(1), 92-7. Journal code: 8509412. ISSN:0910-5050. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 2937762 AN 86167767 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Experimental combined hormone therapy with tamoxifen, aminoglutethimide and medroxyprogesterone acetate was investigated using three hormone-dependent human breast carcinomas serially transplanted into nude mice. The antitumor effect of combined tamoxifen and aminoglutethimide was better than that of either tamoxifen or aminoglutethimide alone. Since aminoglutethimide significantly reduced the level of estrogen and the uterine weight in normal female mice, the antitumor effect of combined tamoxifen and aminoglutethimide was assumed to be a result of the low estrogen level produced by aminoglutethimide, favoring the competition of tamoxifen with estrogen receptors. There was no additive antitumor effect of the combination of tamoxifen and medroxyprogesterone acetate, although serum medroxyprogesterone acetate levels in nude mice were almost equivalent to those of humans. These results indicate that combination hormone therapy, especially with and aminoglutethimide, might be a promising method for clinical application.

Answer 5:

Bibliographic Information

The control of human pancreatic adenocarcinoma xenografts in nude mice by hormone therapy. Greenway B; Duke D; Pym B; Iqbal M J; Johnson P J; Williams R The British journal of surgery (1982), 69(10), 595-7. Journal code: 0372553. ISSN:0007-1323. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 7127040 AN 83023935 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine

on SciFinder (R))